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Regional and socioeconomic variation in survival of melanoma patients in Denmark

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ABSTRACT

INTRODUCTION: This article explores variation in survival and mortality of Danish melanoma patients from 2012 to 2017 in relation to their region of residence and socioeconomic status.

METHODS: Data were extracted from The Danish Melanoma Database, a clinical register, based on reports from hospital departments and dermatologists, and designed for quality improvement. The analysis included covariates at the person and tumour level. A cohort analysis was implemented to quantify the variations and identify the underlying mechanisms behind regional and socioeconomic variations in mortality of melanoma patients.

RESULTS: The mortality of melanoma patients varied between the five regions with mean hazard ratios (95% confidence interval) of 1.36 (1.07-1.74) in men and 1.44 (1.08-1.92) in women between the regions with highest and lowest mortality. Mortality was highest in the patients with the lowest income and shortest education. Regional variation in mortality was attributable to underlying variation in tumour stage and thickness, and it was not confounded by other covariates.

CONCLUSIONS: The two regions with the lowest mortality (highest survival) had high absolute incidence rates of stage IA and thin melanomas, indicating a high level of diagnostic activity in these regions. There was no regional variation in the incidence of advanced melanoma. The optimal level of diagnostic investigation of skin lesions has yet to be established.

FUNDING: none.

TRIAL REGISTRATION: not relevant.

Melanoma is a malignant cancer that arises in the melanocyte, a pigmented cell type that exists in many organs and tissues, but most predominantly in the skin. International Classification of Diseases, tenth version (ICD-10) code C43 identifies melanoma of the skin, and this is the disease entity used in most epidemiological melanoma research.

Important adverse prognostic factors include male sex, larger Breslow thickness, ulceration of the tumour epithelium and a higher stage [1].

According to population-based cancer registration in Denmark [2], the annual incidence of melanoma of the skin in 2012-2016 was 900 in men and 1,042 in women. The disease can be progressive and fatal, but the annual numbers of deaths certified as caused by skin melanoma were much lower, 139 in men and 101 in women. Incidence rates have increased in Europe in recent decades [3, 4], and survival has improved in the same period [5].

The risk of melanoma is related to sun exposure, especially intermittent sunburn and exposure in childhood, but it is also related to other sources of ultraviolet radiation such as the use of sun beds [6].

The primary treatment for melanoma of the skin is surgical excision of the tumour including a safety margin of surrounding tissue, and staging of the disease by excision of the directly draining lymph node(s) (sentinel node). For tumours included in this study, sentinel node biopsy was generally performed in tumours with a thickness of 1.0 mm or more, or if ulcerated or with dermal mitoses. Loco-regional metastases and distant oligo-metastatic disease may be treated surgically. Advanced cancer is treated with systemic immunotherapy or targeted therapy. These modalities have shown remarkably good efficacy in advanced melanoma in recent years, with prolonged survival an even occasionally complete response, with patients potentially being cured [7].

The principal epidemiological analyses in this report address the all-cause mortality of patients with melanoma of the skin in relation to their region of residence and their socioeconomic status. The five government regions in Denmark are budget-holders and operationally responsible for the management and provision of healthcare services for their respective populations, and the comparison of the survival of their resident cancer patients is therefore relevant to the evaluation of their services and may serve to inform quality improvement initiatives.

METHODS

The present analyses used 13,817 cases of melanoma of the skin (C43) diagnosed in the period from 2012 to 2017 in the RKKP clinical database for skin melanoma:

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TABLE 1 / Cox regression analyses of all-cause mortality in relation to the available variables on male and female melanoma patients, Denmark, 2012-2017[a].

	Men (N = 6,444)			Women (N = 7,373)		
	n	HR, mean (95% CI)	p-value	n	HR, mean (95% CI)	p-value
Year of diagnosis[b]			0.04			0.90
2012	1,011	1.00 (ref.)		1,104	1.00 (ref.)	
2013	945	1.06 (0.87-1.29)		1,180	0.94 (0.74-1.20)	
2014	1,048	0.84 (0.68-1.04)		1,237	0.99 (0.77-1.28)	
2015	1,009	0.88 (0.70-1.10)		1,231	0.90 (0.68-1.19)	
2016	1,207	0.76 (0.60-0.97)		1,376	0.98 (0.73-1.31)	
2017	1,224	0.74 (0.55-1.01)		1,245	0.81 (0.54-1.23)	
Age group, yrs			< 0.0001			< 0.0001
≤ 29	195	0.08 (0.01-0.60)		470	0.14 (0.05-0.45)	
30-39	391	0.33 (0.15-0.71)		761	0.18 (0.08-0.42)	
40-49	802	0.40 (0.24-0.67)		1,374	0.31 (0.18-0.54)	
50-59	1,037	0.62 (0.42-0.92)		1,287	0.53 (0.33-0.85)	
60-69	1,605	1.00 (ref.)		1,450	1.00 (ref.)	
70-79	1,672	2.11 (1.63-2.74)		1,206	1.81 (1.29-2.54)	
≥ 80	742	6.91 (5.37-8.87)		825	6.35 (4.72-8.55)	
Charlson Comorbidity Index			< 0.0001			< 0.0001
0	4,506	1.00 (ref.)		5,682	1.00 (ref.)	
1-2	1,307	1.44 (1.23-1.69)		1,271	1.66 (1.37-2.01)	
≥ 3	631	2.47 (2.08-2.94)		420	3.09 (2.48-3.86)	
Region of residence			0.03			0.09
North Denmark Region	553	1.36 (1.07-1.74)		637	1.44 (1.08-1.92)	
Central Denmark Region	1,099	1.23 (1.02-1.49)		1,325	1.15 (0.92-1.45)	
Region of Southern Denmark	1,528	1.07 (0.90-1.29)		1,846	1.05 (0.85-1.31)	
Region Zealand	930	1.27 (1.04-1.56)		1,025	1.26 (0.98-1.62)	
Capital Region of Denmark	2,334	1.00 (ref.)		2,540	1.00 (ref.)	
Civil status			< 0.0001			0.008
Married	4,426	1.00 (ref.)		3,995	1.00 (ref.)	
Cohabiting	1,262	1.53 (1.32-1.79)		2,130	1.17 (0.96-1.43)	
Single	756	1.20 (0.88-1.63)		1,248	1.70 (1.20-2.42)	
Education			< 0.0004		1.00 (ref.)	0.08
School	1,317	1.00 (ref.)		1,734	0.85 (0.70-1.02)	
Professional education	2,946	0.85 (0.72-0.99)		2,952	0.70 (0.54-0.90)	
Shorter further education	1,316	0.64 (0.51-0.79)		1,985	0.78 (0.46-1.30)	
Longer further education	747	0.68 (0.51-0.89)		587	0.88 (0.61-1.29)	
Unknown	118	0.86 (0.60-1.23)		115		
Income			< 0.0001			0.12
Quartile 1	1,611	1.00 (ref.)		1,844	1.00 (ref.)	
Quartile 2	1,611	0.93 (0.80-1.09)		1,843	1.01 (0.84-1.21)	
Quartile 3	1,611	0.73 (0.60-0.90)		1,843	0.80 (0.61-1.05)	
Quartile 4	1,611	0.60 (0.47-0.76)		1,843	0.77 (0.58-1.02)	
Tumour stage			< 0.0001			< 0.0001
IA	3,001	1.00 (ref.)		3,870	1.00 (ref.)	
IB	1,286	1.47 (1.17-1.85)		1,556	1.20 (0.89-1.60)	
IIA	482	2.21 (1.70-2.87)		513	2.29 (1.71-3.08)	
IIB	307	3.16 (2.45-4.08)		265	4.28 (3.23-5.68)	
IIC	198	5.27 (4.09-6.78)		164	5.73 (4.27-7.69)	
III	678	4.47 (3.63-5.52)		507	5.81 (4.47-7.55)	
IV	93	17.00 (12.71-22.74)		47	17.00 (11.14-25.97)	
Unknown	399	2.13 (1.62-2.80)		451	1.59 (1.11-2.26)	
Breslow thickness, mm			< 0.0001			< 0.0001
0-1	3,622	1.00 (ref.)		4,590	1.00 (ref.)	
1-2	1,200	1.72 (1.41-2.12)		1,354	1.47 (1.14-1.90)	
> 2	1,226	3.85 (3.28-4.52)		968	4.13 (3.39-5.03)	
Unknown	396	1.96 (1.51-2.53)		461	1.85 (1.36-2.52)	

CI = confidence interval; HR = hazard ratio; ref. = reference.

a) Supplementary material gives more detailed tabulations of covariates in the five regions, contact the correspondence author.

b) p < 0.0001.

CONTINUES »

TABLE 1 CONTINUED / Cox regression analyses of all-cause mortality in relation to the available variables on male and female melanoma patients, Denmark, 2012-2017[a].

	Men (N = 6,444)			Women (N = 7,373)		
	n	HR, mean (95% CI)	p-value	n	HR, mean (95% CI)	p-value
Anatomic site			< 0.0001			0.02
Head and neck	1,080	1.17 (0.96-1.48)		764	1.21 (0.97-1.50)	
Back	2,558	1.16 (0.97-1.40)		1,817	1.21 (0.98-1.51)	
Front	1,047	1.08 (0.86-1.37)		689	1.22 (0.86-1.73)	
Extremities	1,606	1.00 (ref.)		3,915	1.00 (ref.)	
Genitals or unknown	153	1.83 (1.31-2.55)		188	1.74 (1.21-2.50)	
Morphology			< 0.0001			< 0.0001
Lentigo malignant melanoma	279	1.00 (ref.)		265	1.00 (ref.)	
Nodular melanoma	611	2.56 (2.16-3.05)		571	2.42 (1.96-2.98)	
Superficially spreading melanoma	4,964	1.13 (0.86-1.48)		5,863	0.89 (0.64-1.23)	
Other or unknown	590	1.71 (1.41-2.08)		674	1.90 (1.51-2.39)	

CI = confidence interval; HR = hazard ratio; ref. = reference.
a) Supplementary material gives more detailed tabulations of covariates in the five regions, contact the correspondence author.
b) p < 0.0001.

The Danish Melanoma Database [8]. The data are based on reports from hospital departments and practicing dermatologists and were validated against the Danish Pathology Register.

Data on household income, education, civil status, and comorbidity were obtained by linkage to Statistics Denmark, the Central Person Register and the National Hospital Discharge Register, respectively [9-11].

Household income per person in the year before cancer diagnosis was analysed by quartiles of the income distribution for melanoma patients, separately for men and women. The highest attained education for each person was classified as either basic school education (the compulsory school education only); professional education (including for example apprenticeships and including high-school only); shorter further education; and longer further education. Civil status was classified as married or in registered partnership; other cohabiting persons; single. Comorbidity was characterised by the Charlson Index, computed on the basis of hospital discharge diagnoses in the ten-year period leading up to the cancer diagnosis. Missing values were analysed as a separate category.

A cohort analysis was conducted of the occurrence of deaths in relation to time at risk from date of diagnosis until death, emigration or end-of-follow-up on 8 October 2018, whichever occurred first. This was implemented as a Cox regression model using time since date of diagnosis as the principal time dimension. Analyses were conducted for men and women separately, and the basic models included age (continuous quadratic function to account for the non-linear association between age and mortality), sex and year of diagnosis (categorical) as covariates. Further covariates were added separately to the basic model to identify confounding or mediating characteristics.

Trial registration: not relevant.

RESULTS

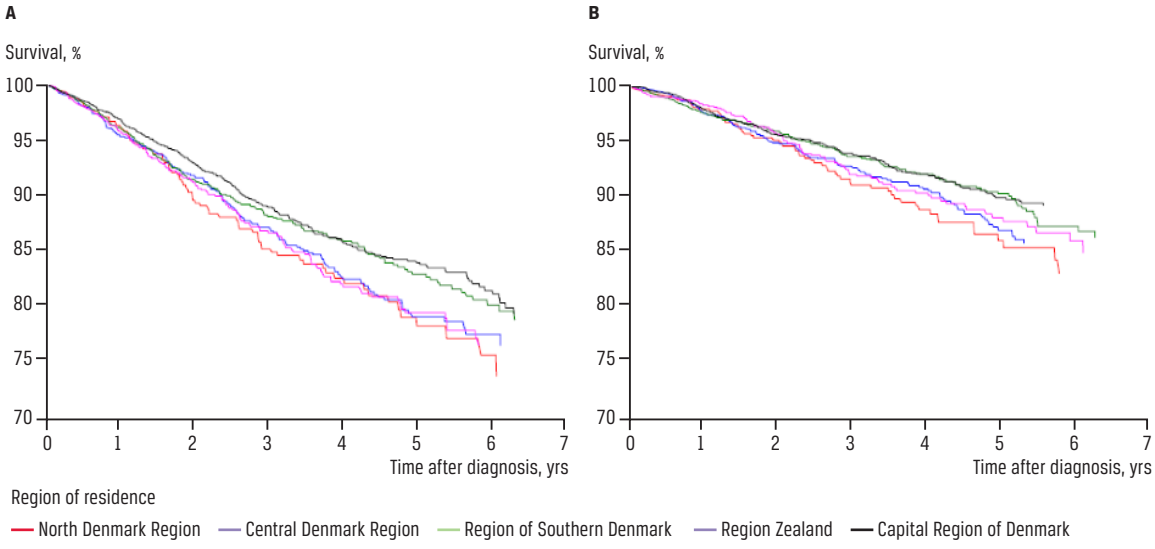
Table 1 shows the distributions of covariates among male and female patients. The overall distributions of age, comorbidity, stage, Breslow thickness, anatomic localisation and histology were as one would expect in a population-based cohort of melanoma patients.

Incidence rates of melanoma differed between regions. The highest incidence for both sexes occurring in The Capital Region and The Region of Southern Denmark, and the lowest in the North Denmark Region and in The Central Denmark Region. Mortality rates were more similar in the regions, but lowest in The Capital Region, especially in women. In both sexes, The Capital Region had the highest proportions of younger patients, patients with stage IA melanoma, patients with thin lesions and patients with superficially spreading melanoma.

Figure 1 shows the Kaplan-Meier survival functions for all-cause mortality of male and female melanoma patients. Regional variation in survival emerged gradually over the six-year follow-up period. Log-rank tests were $p = 0.04$ and $p = 0.07$ for men and women, respectively. Survival was highest among the patients of The Capital Region and The Region of Southern Denmark, lower in The Central Denmark Region and The Zealand Region, and lowest in the North Denmark Region.

Table 1 presents the results from regression analyses, with each variable analysed separately, but ad-

FIGURE 1 / Kaplan-Meier survival functions for death from any cause among male (**A**) and female (**B**) melanoma patients in Denmark, 2012-2017.



justed for year of diagnosis, age and comorbidity. Mortality rates were highest in older persons and persons with comorbidity, advanced stage, thick melanoma, nodular melanoma or localisation on the head or trunk (and lowest when on the extremities). Mortality decreased with calendar time of diagnosis, but this trend was only statistically significant in men. Mortality was lowest in persons with a high education or a high income. This trend was statistically significant in men. Married persons had a lower mortality than cohabiting and single persons. Comparison of the regions showed small differences in the mortality of melanoma patients, but consistent with the Kaplan-Meier estimates with the highest mortality in men and women in The North Denmark Region, intermediate in the Central Denmark Region and in Region Zealand, and lowest in The Region of Southern Denmark and The Capital Region.

Table 2 provides more detail on the variation in mortality between patients in the five regions. The excess mortality rates in patients in The North Denmark Region and the Central Denmark Region were much attenuated when estimates were adjusted for tumour stage or for Breslow thickness. The excess mortality in men and women in Region Zealand was mostly observed in men, but it was not very strong, and it was attributable to stage and thickness. However, for women, the excess mortality was more strongly attributable to these two variables. In fully adjusted regression models, the variation between patients residing in different regions was much reduced, and the variables that explain this reduction were tumour thickness and stage.

Unlike the variation between regions, the magnitude of the variation between income groups was not sensitive to adjustment for available covariates (data not shown).

DISCUSSION

The variation in mortality of melanoma patients between Danish regions was most strongly associated with variation in tumour stage and thickness; and the favourable case-mix in the Capital Region and Region of Southern Denmark was possibly owed to more intensive diagnostic investigation in these regions. The Capital Region, especially, has more practicing dermatologists than the remaining regions [12].

The results are consistent with a scenario in which increased diagnostic intensity enriches the patient population with thin melanoma and stage IA melanoma, including a subgroup of cancers that are slow-growing, and probably would not be diagnosed in the lifetime of the person if the diagnostic intensity had been lower [13]. This leads to a pattern of increased population incidence, more favourable case-mix, and a lower patient mortality, but no reduction in the population rate of occurrence of fatal melanomas and no reduction in the population mortality rate. A study from the US analysed skin biopsy rates and melanoma incidence and mortality in nine geographical areas [14]. A strong association was found between biopsy rates and incidence rates. The excess rate attributable to biopsy rates was confined to early-stage cancers, and there was no association with advanced melanomas or with melanoma mortality.

TABLE 2 / Cox regression analyses of all-cause mortality in relation to region of residence of male and female melanoma patients, Denmark, 2012-2017. Sensitivity analyses for available covariates. The values are mean hazard ratio (95% confidence interval)[a].

	Model 1[b] (p = 0.03/0.09)[c]	Model 1[b] + civil status (p = 0.02/0.06)[c]	Model 1[b] + education (p = 0.06/0.12)[c]	Model 1[b] + income (p = 0.06/0.14)[c]	Model 1[b] + tumour stage (p = 0.17/0.92)[c]	Model 1[b] + Breslow thickness (p = 0.47/0.51)[c]	Model 1[b] + anatomic site (p = 0.02/0.06)[c]	Model 1[b] + morphology (p = 0.08/0.10)[c]	All covariates (p = 0.58/0.83)[c]
Males									
North Denmark Region	1.36 (1.07-1.74)	1.37 (1.07-1.74)	1.31 (1.02-1.67)	1.29 (1.01-1.65)	1.22 (0.96-1.56)	1.14 (0.90-1.46)	1.36 (1.07-1.74)	1.28 (1.01-1.64)	1.09 (0.85-1.40)
Central Denmark Region	1.23 (1.02-1.49)	1.24 (1.02-1.50)	1.20 (0.99-1.46)	1.19 (0.98-1.44)	0.96 (0.79-1.17)	1.08 (0.89-1.31)	1.22 (1.01-1.48)	1.13 (0.93-1.37)	0.99 (0.81-1.21)
Region of Southern Denmark	1.07 (0.90-1.29)	1.10 (0.92-1.31)	1.03 (0.86-1.23)	1.00 (0.83-1.20)	1.07 (0.89-1.29)	1.02 (0.85-1.23)	1.02 (0.85-1.23)	1.03 (0.85-1.23)	0.99 (0.82-1.20)
Region Zealand	1.27 (1.04-1.56)	1.29 (1.06-1.59)	1.24 (1.01-1.52)	1.22 (0.99-1.50)	1.21 (0.98-1.48)	1.19 (0.97-1.46)	1.26 (1.03-1.55)	1.26 (1.03-1.55)	1.15 (0.94-1.42)
Capital Region of Denmark	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Females									
North Denmark Region	1.44 (1.08-1.92)	1.46 (1.09-1.94)	1.40 (1.05-1.86)	1.39 (1.04-1.86)	1.11 (0.83-1.48)	1.24 (0.93-1.66)	1.44 (1.08-1.91)	1.40 (1.05-1.87)	1.11 (0.82-1.49)
Central Denmark Region	1.15 (0.92-1.45)	1.17 (0.93-1.47)	1.13 (0.90-1.42)	1.14 (0.90-1.43)	1.06 (0.84-1.34)	1.13 (0.90-1.42)	1.18 (0.94-1.49)	1.16 (0.92-1.46)	1.12 (0.88-1.42)
Region of Southern Denmark	1.05 (0.85-1.31)	1.06 (0.85-1.32)	1.00 (0.80-1.25)	1.02 (0.81-1.27)	1.08 (0.87-1.35)	1.02 (0.82-1.27)	1.01 (0.81-1.26)	1.05 (0.84-1.31)	1.05 (0.83-1.33)
Region Zealand	1.26 (0.98-1.62)	1.28 (1.00-1.65)	1.22 (0.94-1.57)	1.22 (0.94-1.57)	0.99 (0.77-1.28)	1.15 (0.90-1.49)	1.26 (0.98-1.62)	1.28 (0.99-1.65)	0.97 (0.74-1.26)
Capital Region of Denmark	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)

ref. = reference.

a) Supplementary material gives more detailed tabulations of covariates in the five regions, contact the correspondence author.

b) Model 1 includes age, year of diagnosis and Charlson Comorbidity Index.

c) Males/females.

The country with the historically highest melanoma incidence rate in the world is Australia [15]. This is mainly attributable to extreme sunlight exposure in the susceptible Caucasian population [16]. Australia had incidence rates of 40.4 per 100,000 in males and 28.6 per 100,000 in females in 2008-2012 [15]. It is remarkable that in the same period (2008-2012), Danish women in the Capital Region and the Region of Southern Denmark had similar or higher incidence rates than women in Australia (the Capital Region 34.4; the Region of Southern Denmark 28.3 [2] versus Australia 28.6 [15]). Apart from differences in diagnostic activity, comparison between countries may be complicated by different patterns of exposure, e.g. ambient sunlight, sun-seeking behaviour and summer holidays, and use of sun beds which may vary between countries [6, 16].

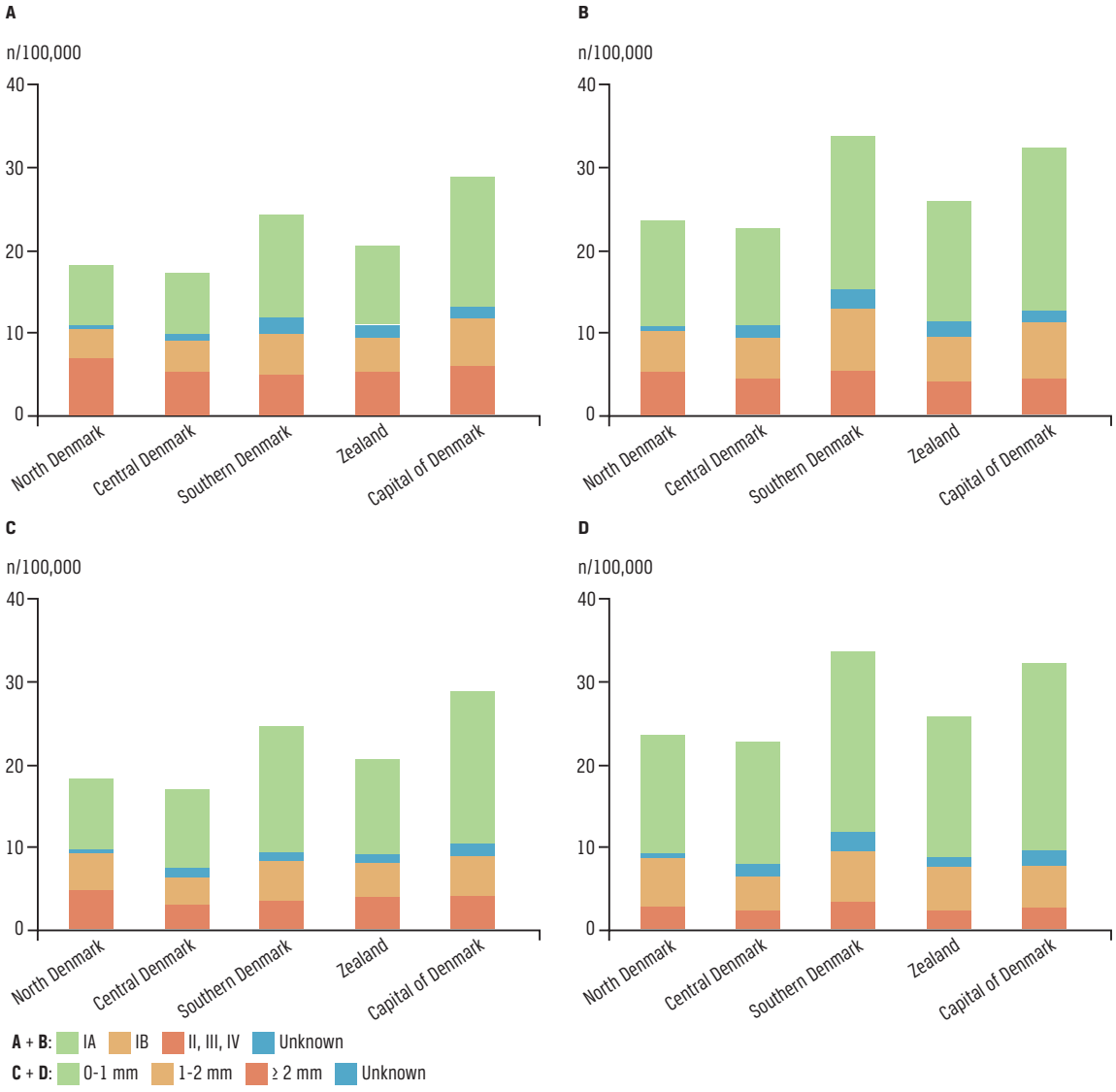
We found a strong association between personal income and mortality for male patients, but a weaker association for women. The association was not sensitive to adjustment for person- and tumour characteristics. We cannot exclude that the association in men may be dominated by the general difference in life expectancy between socioeconomic groups rather than by a differential mortality from the melanoma. This might be improved by considering melanoma-specific mortality instead of all-cause mortality.

In a recent Danish study, an increased risk of being diagnosed with melanoma at a more advanced stage was found among patients with lower education and lower income [17]. These findings are based on combined analysis of men and women and are consistent with the present study results.

Figure 2 presents the age-standardised rates of categories of stage and Breslow thickness in Denmark's five regions. The lasting impression is that the variable rates of stage IA cancers and thin melanoma explain the overall difference in incidence between the regions, whereas the rates of advanced cancers and thick melanoma are constant.

Although these results are indicative of a high intensity of diagnostic intervention in the Capital Region and the Southern Denmark Region, and suggestive of a possible over-diagnosis scenario, the importance of early detection must be emphasised. Data from Australia show that about 24% of melanoma deaths were preceded by diagnosis of melanoma with a Breslow thickness of 1 mm or less [18]. It cannot be assumed that stage IA and thin melanoma are harmless. A recent analysis from Sydney, Australia of more than 6,000

FIGURE 2 / Stacked bar charts of age-standardised incidence rates per 100,000 of tumour stage IA, IB, and II, III, IV, (**A** men, **B** women) and of categories of Breslow thickness (**C** men, **D** women) in Danish regions, 2012-2017.



melanoma patients showed that melanoma with a thickness of 0.8-1.0 mm carried a higher long-term mortality than thinner melanoma [19]. This signals the need to develop prognostic markers of long-term outcomes in stage I and thin melanoma.

The present analysis does not include details on the surgical and other oncological treatment of each patient, and these data do not rule out a role of treatment variation in the observed variation in mortality. The initial treatment is likely to be similar in the regions, with surgical excision being the primary treatment of almost all patients.

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A more extensive reference list is available from the correspondence author.